Pearls of Pediatric Pulmonology

Brian R Wingrove, MHS, PA-C, DFAAPA
Children's Physician Group – Pulmonology at Scottish Rite
Children's Healthcare of Atlanta

1

Disclosures

I have no financial or legal associations to disclose

Objectives

1. Review pathophysiology of cystic fibrosis and learn the new drugs available for patients
2. State indications for RSV prophylaxis
3. Identify the newest developments in asthma therapy and review the latest GINA recommendations
4. Describe morbidity associated with pediatric OSA and appropriate interventions

3

What is asthma?

"Asthma is a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role: in particular, mast cells, eosiniphils, T lymphocytes, macrophages, neutrophils, and epithelial cells. In susceptible individuals, this inflammation causes recurrent episodes of wheezing, breathlessness, chest tightness, and coughing, particularly at night or in the early morning. These episodes are associated with widespread but variable airflow obstruction that is often reversible either spontaneously or with treatment. The inflammation also causes an associated increase in the existing bronchial hyperresponsiveness to a variety of stimuli. Reversibility of airflow limitation may be incomplete in some patients with asthma."

4

What is Asthma?

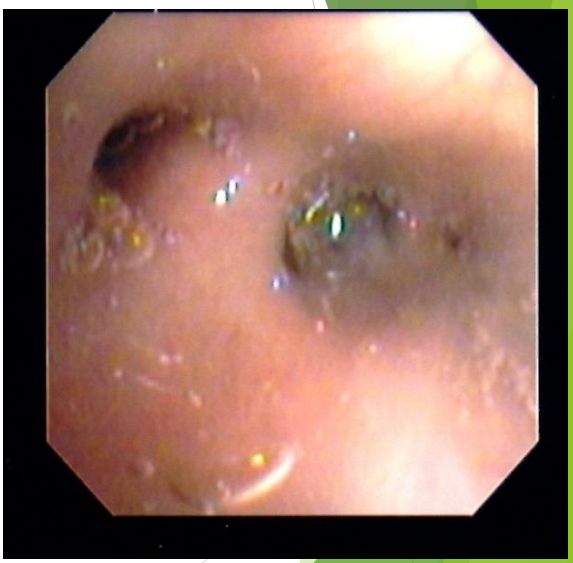
Asthma is a chronic inflammatory disorder of the airways which causes recurrent episodes of wheezing, breathlessness, chest tightness, and coughing, particularly at night or in the early morning. These episodes are often reversible either spontaneously or with treatment.

5

What is Asthma?

Asthma is chronic inflammation of the airways that causes symptoms like coughing or wheezing that gets better with albuterol.

6



7

Asthma Prevalence

- Prevalence among children – 8.4% (greater than adults - 7.6%)
- Highest among poor children – 11.1%
- Boys – 9.9% (6.9% of girls)
- Non-Hispanic black children – 10.3%

- 2015 CDC Data

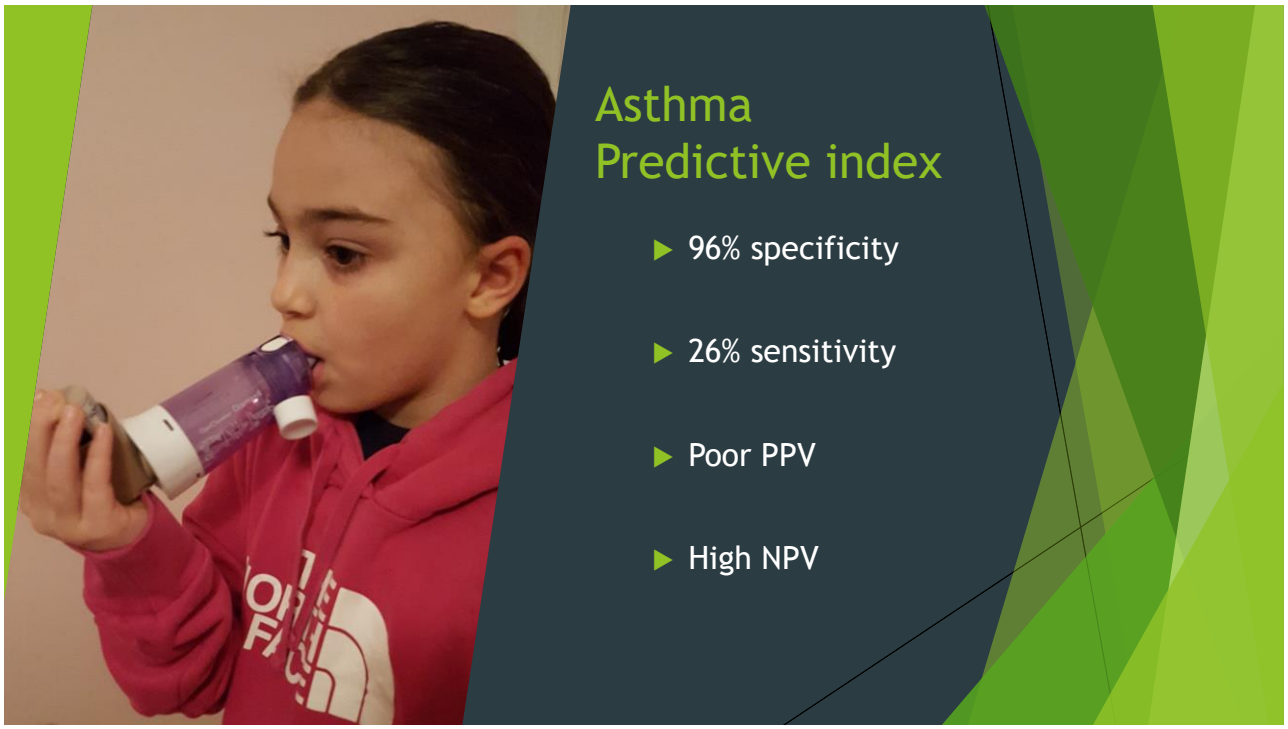
8

Risk Factors – Asthma Predictive Index

2 – 3 episodes of wheezing in the past year

MAJOR	MINOR
Atopic dermatitis	Allergic Rhinitis
Food Allergy	Eosinophilia
Family history of asthma	Wheezing without colds

9


Asthma
Predictive index
96% specificity
26% sensitivity
Poor PPV
High NPV

10

Pediatric Asthma Risk Score

PARS

- Cincinnati Childhood Allergy and Air Pollution Study (CCAAPS)
- 762 infants born 2001-2003 in Cincinnati,OH and North Kentucky
- Parents with documented atopy (>1 allergy symptom and skin prick testing positive (SPT) to > 1 aeroallergen)
- Annual exams at ages 1,2,3,4, and 7 years-old
  - Monitored for allergy symptoms at each visit: wheezing apart from colds, eczema, rhinitis, skin prick testing
  - 7 year-old visit – objective evaluation for asthma

Skin Allergy Test

Pediatric Asthma Risk Score

	Nonasthmatic subjects (n = 494)	Asthmatic subjects (n = 95)	*P* value*
Clinical risk factors			
Eczema before age 3 y	24.0% (118)	42.6% (40)	.0004
Wheezing apart from colds	12.0% (59)	45.3% (43)	<.0001
Early wheezing (before age 3 y)	29.4% (145)	68.4% (65)	<.0001
Early frequent wheezing	10.3% (51)	37.9% (36)	<.0001
AR (clinician's diagnosis probable or definite)	35.1% (172)	52.7% (49)	.0016
Positive SPT response to ≥1 aeroallergen	53.5% (264)	71.6% (68)	.0009
Positive SPT response to ≥1 food allergen	16.2% (80)	26.3% (25)	.02
Positive SPT response to aeroallergens/food allergens (≥2 positive SPT response)	38.3% (189)	60.0% (57)	.0001
Personal risk factors			
Parental asthma	37.7% (186)	56.8% (54)	.0005
African American race	19.4% (96)	36.8% (35)	.0004
Male sex	53.6% (265)	61.1% (58)	.18

12

Pediatric Asthma Risk Score (PARS) Sheet

	Possible Scores		
	No	Yes	Child's Score
1. Parental Asthma	0	2	
2. Eczema before age 3 years	0	2	
3. Wheezing apart from colds	0	3	
4. Wheezing before age 3 years	0	3	
5. African-American Race	0	2	
6. SPT positive to ≥ 2 aero and/or food allergens	0	2	
Child's PARS (add lines 1-6 above):			

Patient Score Interpretation

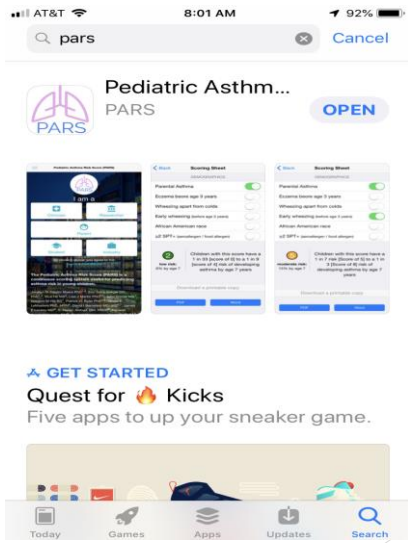
Score	Risk of Asthma by age 7 years		Interpretation
0	3%	LOW RISK	Children with these scores have a 1 in 33 [score of 0] to a 1 in 9 [score of 4] risk of developing asthma by age 7 years
2	6%		
3	8%		
4	11%		
5	15%	MODERATE RISK	Children with these scores have a 1 in 7 risk [Score of 5] to a 1 in 3 [Score of 8] risk of developing asthma by age 7 years
6	19%		
7	25%		
8	32%		
9	40%	HIGH RISK	Children with these scores have a 2 in 5 [Score of 9] to a 4 in 5 [Score of 14] risk of developing asthma by age 7 years
10	49%		
11	58%		
12	66%		
14	79%		

13

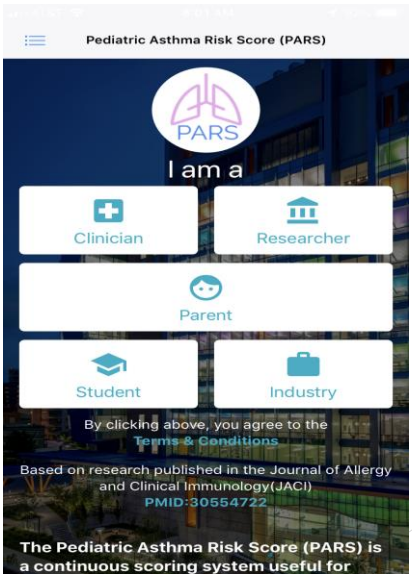
Pediatric Asthma Risk Score

- PARS better for predicting likelihood of developing asthma vs Asthma Predictive Index
- Higher sensitivity and PPV
- Less invasive
- Better predictor for mild-moderate asthma risk patients

Pediatric Asthma Risk Score

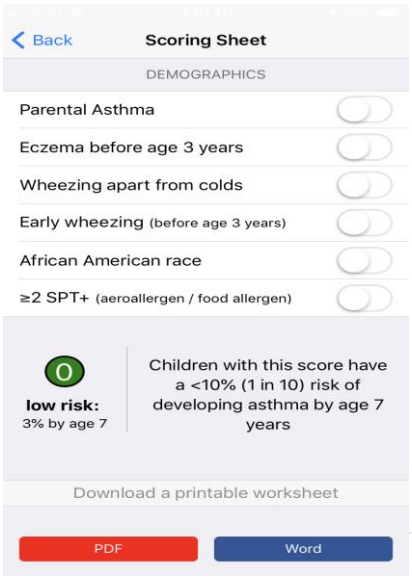


Pediatric Asthma Risk Score

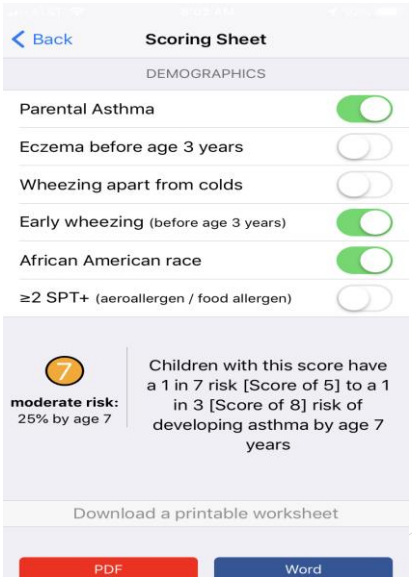


16

Pediatric Asthma Risk Score



Pediatric Asthma Risk Score



GINA Recommendations

- The Global Initiative for Asthma (GINA)
- Increase awareness about asthma
- Improve prevention and management
- Encourage dissemination and implementation of guidelines

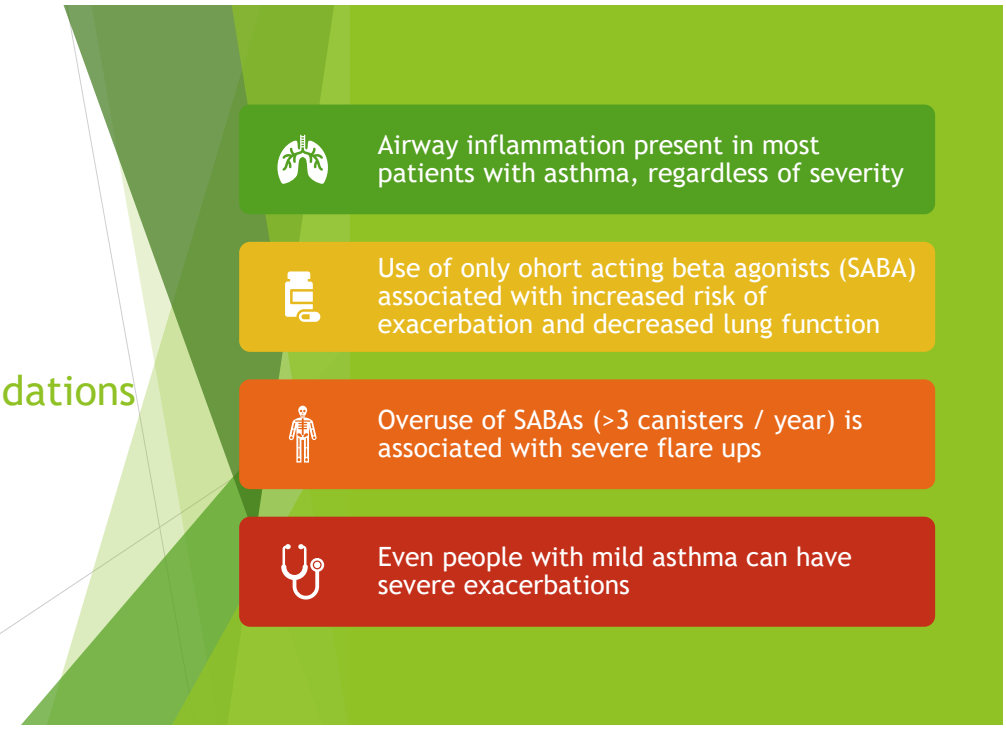
19

GINA Recommendations

- Recommendations released in mid 2019
- Changes for treatment of mild asthma and severe asthma
- Recommendations have not been adopted by the major medical organizations
- Applies to ages 12 years and up

20

GINA Recommendations

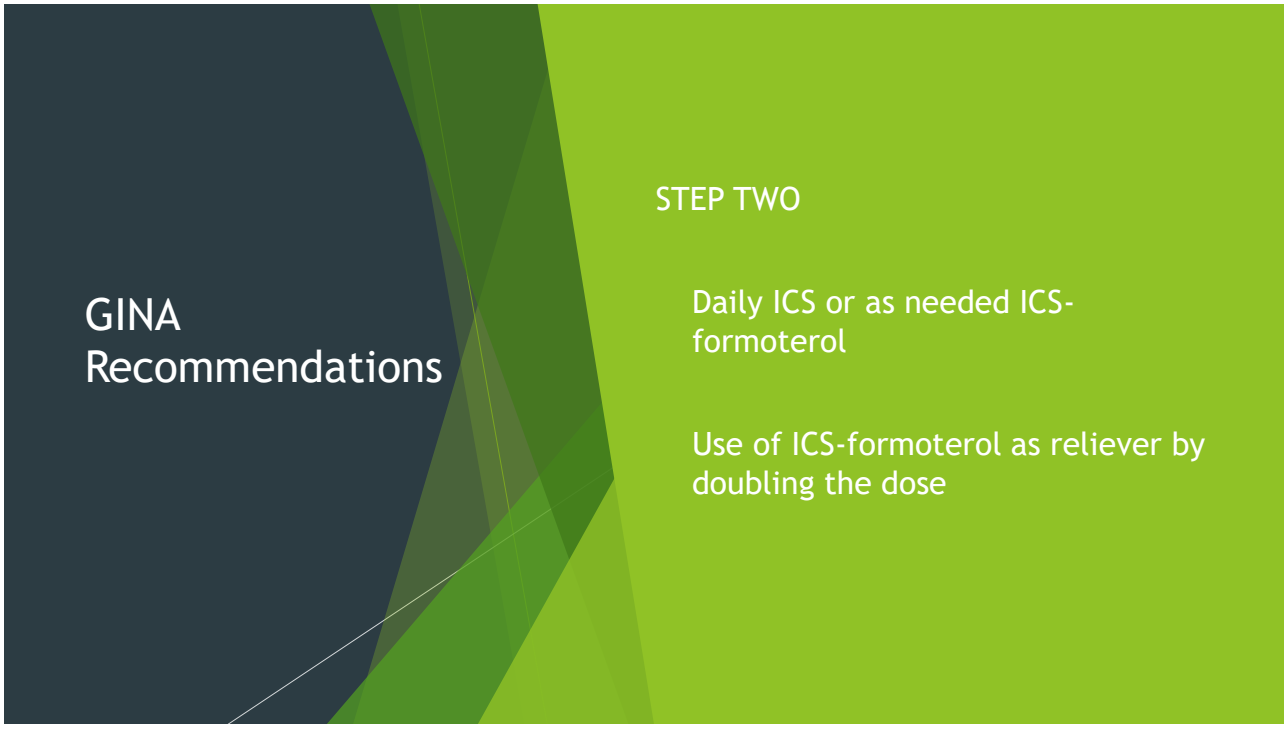


GINA Recommendations

- ALL adults and teens with asthma should receive inhaled corticosteroids (ICS)
- Most people with asthma can be managed with low dose ICS, though responsiveness varies
- Use of low dose ICS effective in preventing exacerbations and improving lung function


GINA
Recommendations
MILD ASTHMA
As needed ICS-formoterol combination
ICS whenever a SABA is taken

23


GINA
Recommendations
STEP TWO
Daily ICS or as needed ICS-formoterol
Use of ICS-formoterol as reliever by doubling the dose

24

GINA Recommendations

STEP THREE – STEP FIVE

Use of daily ICS-formoterol for controller therapy

Use of as needed ICS-formoterol for reliever therapy

25

GINA Recommendations

By using as needed ICS-formoterol, there was a 64% reduction in severe exacerbations

Indirect evidence

Adherence to daily ICS use in mild asthma is poor

26

GINA Recommendations

3 commercially available ICS-long acting beta agonists in the US

- Fluticasone-salmeterol (Advair, AirDuo, Wixela)
- Mometasone-formoterol (Dulera)
- Budesonide-formoterol (Symbicort)

Salmeterol did not perform as well as formoterol

Only budesonide-formoterol combination was studied, but other forms are acceptable in the recommendations

As needed use is off-label

27

What's New in Asthma Therapy

- Flunisolide (Aerospan) – discontinued

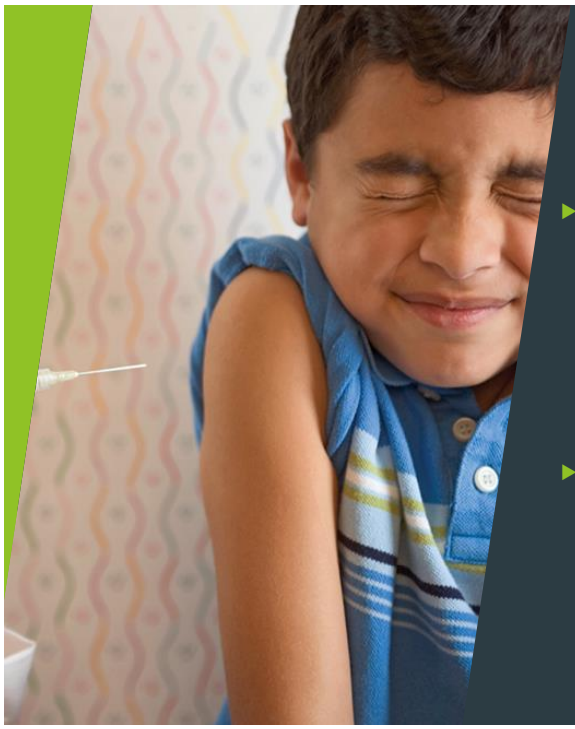
- Fluticasone propionate/Salmeterol (Advair) – now available in generic as AirDuo Respiclick and Wixela Inhub

- Fluticasone propionate DPI (Flovent) – going generic

- Fluticasone furoate (Arnuity Ellipta)

- Beclomethasone (Qvar) – no longer an MDI

28



What's New in Asthma Therapy

- Omalizumab (Xolair)
  - Inhibits IgE binding to mast cells and basophils
  - Given every 2 – 4 weeks
  - Age 8 yrs and older
  - Lowers rate of exacerbations
- Mepolizumab (Nucala)
  - Binds IL-5 reducing production and survival of eosinophils
  - Given every 4 weeks
  - Age 12 yrs and older
  - Reduces exacerbations AND improve FEV1

29

What's New in Asthma Therapy

Benralizumab (Fasenra)

- Binds IL-5 and attracts natural killer cells resulting in depletion of eosinophils
- Given every 4 weeks x 3 doses, then every 8 weeks
- Age 12 yrs and older
- Reduce exacerbations and improve FEV1

Dupilumab (Dupixent)

- Binds IL-4 and IL-13 – reduces inflammation but MOA not established
- Given every 2 weeks
- Age 12 yrs and older
- Reduce exacerbations and improve FEV1

30

Bronchiolitis and Respiratory Syncytial Virus

Bronchiolitis

- Children <2 years of age
- Upper respiratory symptoms followed by lower respiratory infection with inflammation
- Infection with a viral pathogen
- RSV infects up to 70–80% of children <2 years of age each season

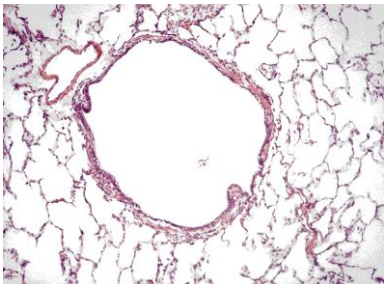
Bronchiolitis

- Viruses infect the terminal bronchiolar epithelial cells
- Cause damage and inflammation in the small bronchi and bronchioles
- Edema, mucus, and sloughed epithelial cells lead to obstruction of small airways and atelectasis
- Pathologic changes occur 18 to 24 hours after infection
- Cell necrosis, ciliary disruption, and peribronchiolar lymphocytic infiltration

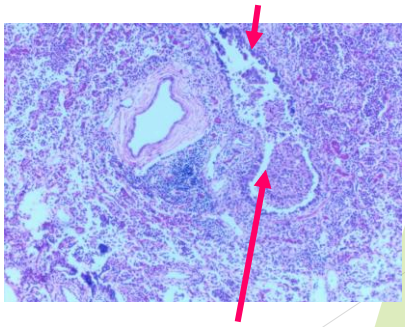
33

Bronchiolitis

Normal Lung



RSV-Infected Lung

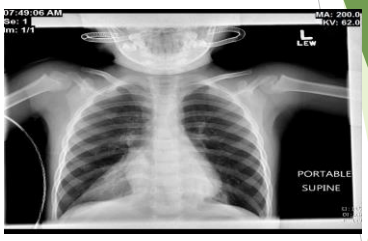


34

Bronchiolits

- Peak incidence at 2 – 6 months of age
- Leading cause of hospitalization among infants
- Significant cause of respiratory disease during the first five years of life
- Fever, rhinorrhea, cough
- Cough, wheezing, crackles
- Apnea
- Respiratory failure

Bronchiolitis and the CXR



- Routine use discouraged
  - 93% are normal
  - 7% airspace disease
  - Unnecessary abx and radiation
  - Adds avoidable cost
- Consider use :
  - RA pulse ox <92%
  - Grunting
  - Focal findings
  - Fever > 39
- Indications for use
  - Severe distress
  - Persistent focal findings
  - Exclude alternative cause
  - Not improving

Bronchiolitis - Treatment

Hypertonic Saline

- Use of 3% hypertonic saline appears to decrease symptoms and LOS by 26%
- Theoretically reverses mucosal edema and decreases thickness of mucus
- Has been shown to increase mucociliary clearance in various situations

37

Bronchiolitis - Treatment

Hypertonic Saline

- Great controversy due to heterogeneity of studies
- Uneven quality of evidence
- No clear benefits seen
- AAP Guideline – May administer to hospitalized patients

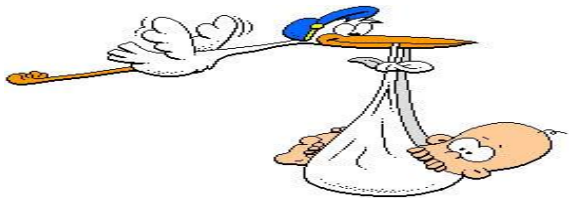
30 weeks Gestational Age

32 weeks Gestational Age

34 weeks Gestational Age

Who Gets Palivizumab?

Infants born at **29 weeks GA** or less who are less than 12 months of age at the start of RSV season



Who Gets Palivizumab?

Infants who are less than 12 months of age with :

- Congenital Airway Abnormalities
- Neuromuscular Disease

Who Gets Palivizumab?

Children under 24 months of age and born before 32 wks GA with chronic lung disease (required oxygen for at least 28 days) AND who have required medical therapy in the last 6 months

Oxygen Diuretics Bronchodilators

Inhaled or Oral Steroids

44

Who Gets Palivizumab?

Children under 12 months of age with hemodynamically significant congenital heart disease

Sleep Disordered Breathing

46

Obstructive Sleep Disordered Breathing

- Spectrum disorder ranging from snoring to Obstructive Sleep Apnea (OSA)
- OSA : Recurrent episodes of partial or complete upper airway obstruction associated with arousals, awakenings and/or desaturations
- Prevalent in 1% - 4% of children
- No differences in gender
- Most common in preschoolers

Obstructive Sleep Apnea

- **Snoring, pausing, gasping**
- Restless sleep
- Night sweats
- Night terrors
- Enuresis
- Morning headaches
- Mouth breathers

48

Obstructive Sleep Apnea

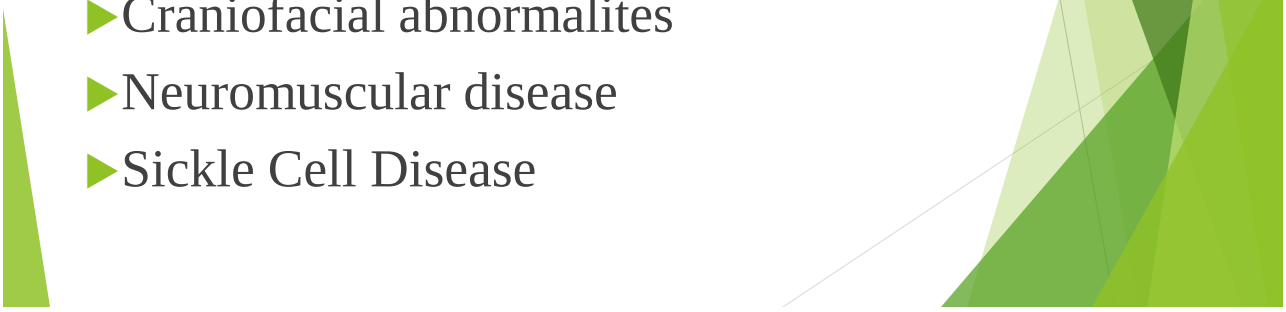
Adverse Sequelae

- Daytime somnolence
- Learning problems
- ADHD
- Aggressive behaviors
- Developmental and growth delays
- Pulmonary hypertension

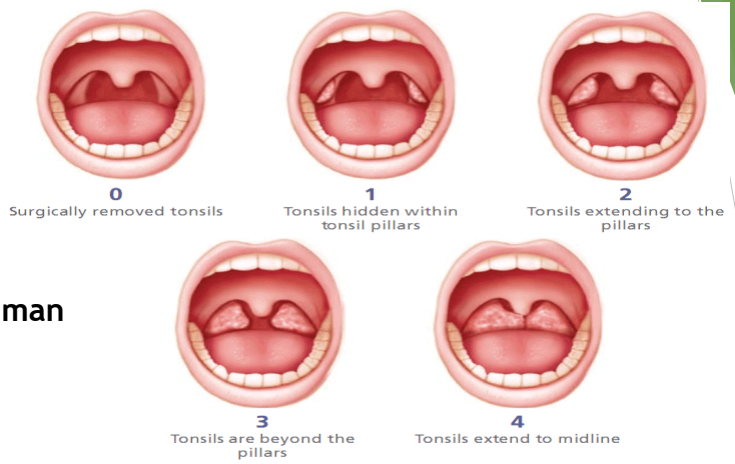
Obstructive Sleep Apnea

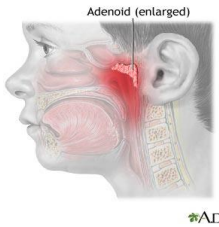
Risk factors

- Adenotonsillar hypertrophy
- Obesity
- Craniofacial abnormalites
- Neuromuscular disease
- Sickle Cell Disease



Brodsky and Friedman Scale





51

Obstructive Sleep Apnea

- Polysomnogram (PSG) is gold standard for diagnosis
- 12 lead study conducted in a monitored lab
- Indicated when clinical assessment suggests OSA
- Arousals more common in children – desats less common
- Challenges : expensive, limited access, placement of electrodes, unfamiliar environment
- Naps not recommended
- Apnea Hypopnea Index (AHI) of >1 or a pattern of obstructive hypoventilation for 25% of time with pCO2 >50

Obstructive Sleep Apnea

Home Sleep Apnea Tests

- Not recommended for children
- Little comparative data between lab tests and home tests
- Underestimation of severity of disease
- No CO2 or arousal monitoring
- Questionable ability of parents to place leads successfully

53

Obstructive Sleep Apnea

- Adenotonsillectomy
- Weight loss
- Craniofacial surgery
- Oxygen supplementation
- CPAP / BiPap
- Intranasal steroids and montelukast
- Spontaneous resolution – Childhood Adenotonsillectomy Trial
  - 194 children aged 5 – 9 years old with mild to moderate OSA
  - After 7 months of observation 42% no longer had OSA
  - Less severe disease, lower waist circumference, fewer symptoms

CYSTIC FIBROSIS

CYSTIC FIBROSIS

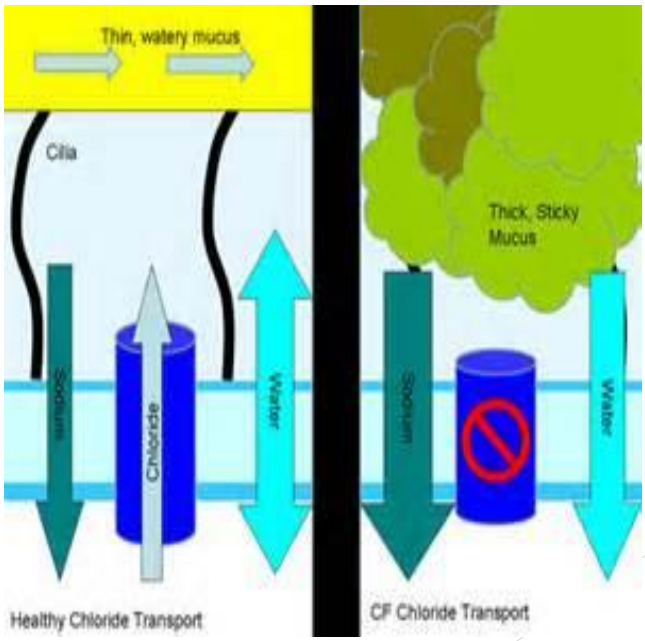
Most common, lethal, inherited disease in Caucasians

An estimated 30,000 children and adults in the United States (70,000 worldwide)

Primarily affects the pulmonary and GI systems

CYSTIC FIBROSIS

- Chloride ions are pumped through channels in cell membranes
- Water follows the movement of the ions
- A defect in the CFTR gene causes problems in the formation and function of anion channels
- As a result water does not go where it is needed
- Mucus becomes very sticky and thick


Thin, watery mucus
Cilia
Sodium
Chloride
Water
Healthy Chloride Transport
Thick, Sticky Mucus
Sodium
Water
CF Chloride Transport

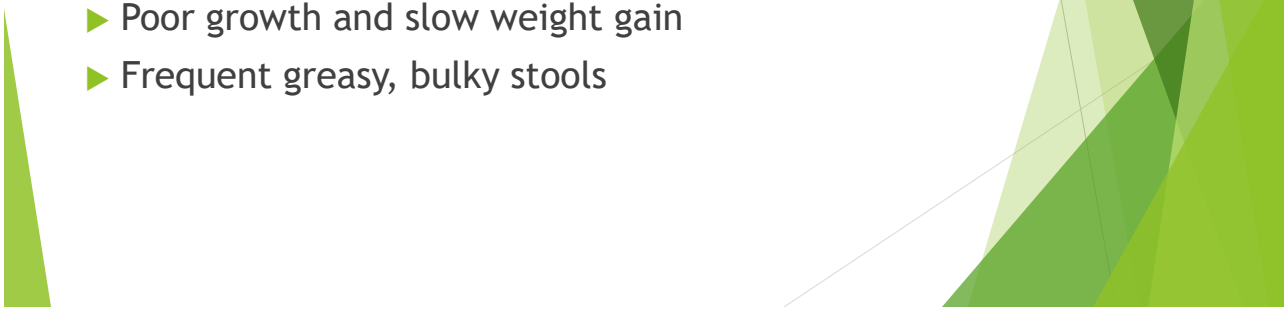
CYSTIC FIBROSIS

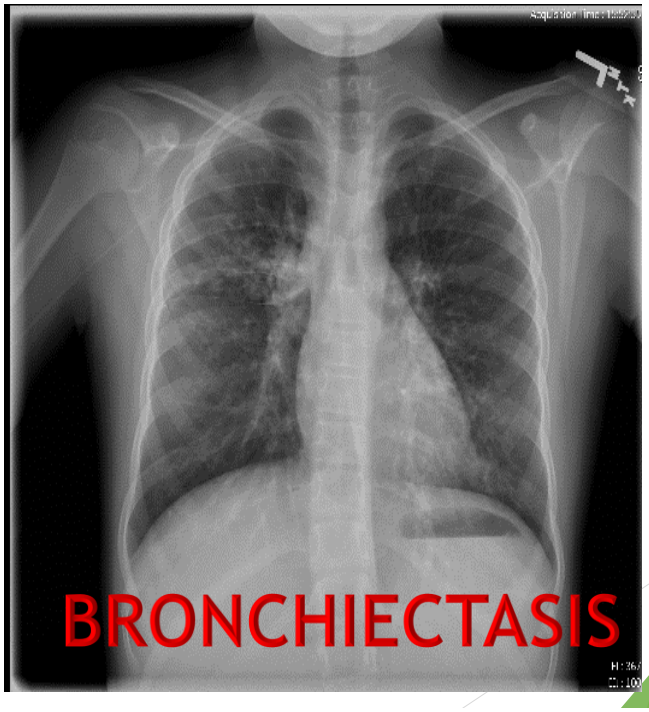
Organ	Pathogenesis	Manifestations	Onset Age	Frequency
Lung	Obstruction/ infection	Bronchiolitis/ Bronchitis/ Bronchiectasis	All	Nearly 100%
Upper airway	Obstruction/ infection	Sinusitis polyps	All	50% 10-15%
Bowel	Obstruction	Meconium ileus DIOS	Birth Late childhood	20% Common
Pancreas	Obstruction	Malabsorption Diabetes	Birth Older	85% 1-5%
Gall bladder	Obstruction	Duct obstruct.	All	20%
Reproductive		Infertility Decr. Fertility	Birth	>99% Common
Joints		Arthritis	Older	Occasional

59

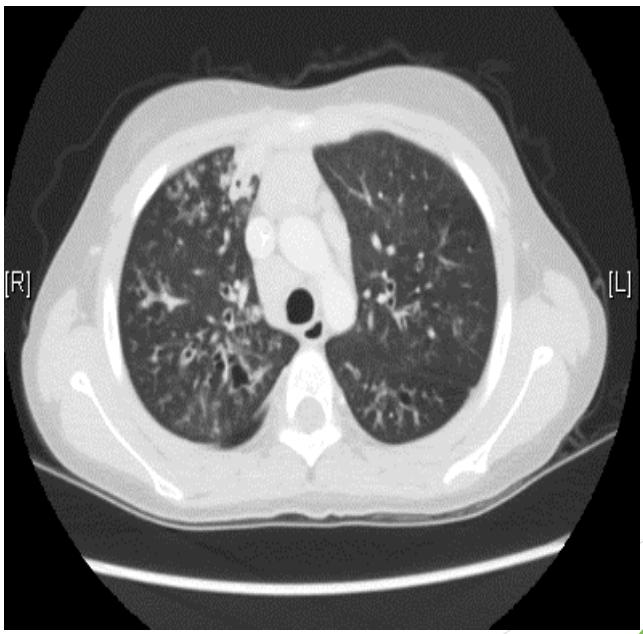
Symptoms of CF

- Persistent coughing
- Frequent lung infections
- Nasal congestion and sinus pain
- Poor growth and slow weight gain
- Frequent greasy, bulky stools





61


[R]
[L]


Clubbed fingers
Normal angle of nail bed
Distorted angle of nail bed
A.D.A.M.

63

Diagnosing CF

- Newborn Screening – ImmunoReactive Trypsinogen (IRT)
- Sweat Chloride Test
- Genetic Testing

Most common mutation is Delta F508

Managing Cystic Fibrosis

- Mobilizing Mucus
  - Chest Physiotherapy (CPT)
  - Bronchodilators
  - Mucolytics
  - Hypertonic Saline
  - Anti-inflammatories

65

Managing Cystic Fibrosis

- Preventing and Treating infections
  - Routine vaccinations
  - Pneumovax
  - Inhaled antibiotics
  - Oral antibiotics
  - IV antibiotics

Managing Cystic Fibrosis

- Maximizing Nutrition
  - Supplemental enzymes
  - Vitamins A, D, E, K
  - High calorie and high protein diets
  - Supplemental nutrition

67

NEW Drugs

- Disease Modifying Drugs (DMD)
  - Potentiators – enhance channel activity
  - Correctors – target folding defects and allow protein to travel
  - Read through – allow ribosomes to ignore end codons to produce full length protein
- Different mutations cause different defects the DMDs are only effective in people with specific mutations
- Delta F508 is a misfolding mutation

NEW Drugs

- Ivacaftor (Kalydeco) 2012
  - Age 6 months and up
  - Any 1 of 38 mutations – not Delta F508
  - Works by keeping the ion transport channel open (potentiator)
  - Increases in FEV1

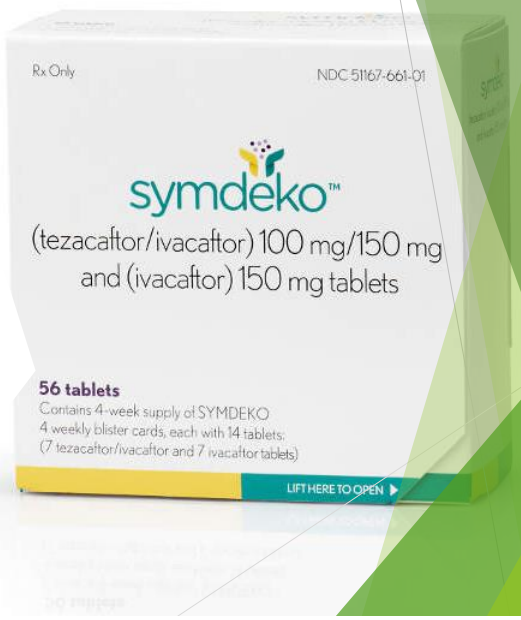
69

NEW Drugs

- Ivacaftor/Lumacaftor (Orkambi) 2015
  - Age 2 years and up
  - 2 copies of the Delta F508 mutation
  - Lumacaftor is a corrector - stabilizes the formation of anion channels and travel
  - Increases in FEV1 and decreases exacerbations
  - Reduction in sweat chloride by 24.8

NEW Drugs

- Ivacaftor / Tezacaftor (Symdeko) 2018
  - Age 6 years and up
  - 2 copies of the Delta F508 mutation, or 1 copy of Delta F508 and 1 other of 26 mutations
  - Helps the CFTR protein to move onto the cell surface and keep the channel open
  - Similar to Orkambi but fewer side effects



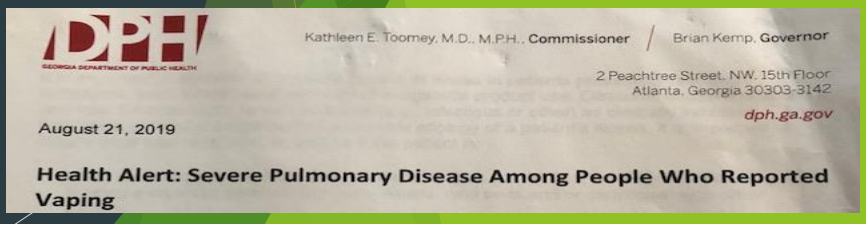
NEW Drugs

- Ivacaftor / Tezacaftor / Elexacaftor (Trikafta) 2019
  - Ages 12 and up
  - Must have at least one copy of Delta F508
  - Elexacaftor even better at correcting protein shape
  - Reduction of sweat chloride to below diagnostic threshold
  - Increase in FEV1 by 10% and reductions in exacerbations
  - Increase in BMI

Vaping

EVALI

- E-cigarette or Vaping product use Associated Lung Injury
- Use surged by 900% among middle and high school students 2011-15
- Dropped in 2016 but increased again 2017-18
- 27.5% of high school students and 10.5% of middle school students
- Pods deliver nicotine salts allowing high levels of nicotine to be inhaled



DPH
GEORGIA DEPARTMENT OF PUBLIC HEALTH

Kathleen E. Toomey, M.D., M.P.H., **Commissioner** / Brian Kemp, **Governor**

2 Peachtree Street, NW, 15th Floor
Atlanta, Georgia 30303-3142
dph.ga.gov

August 21, 2019

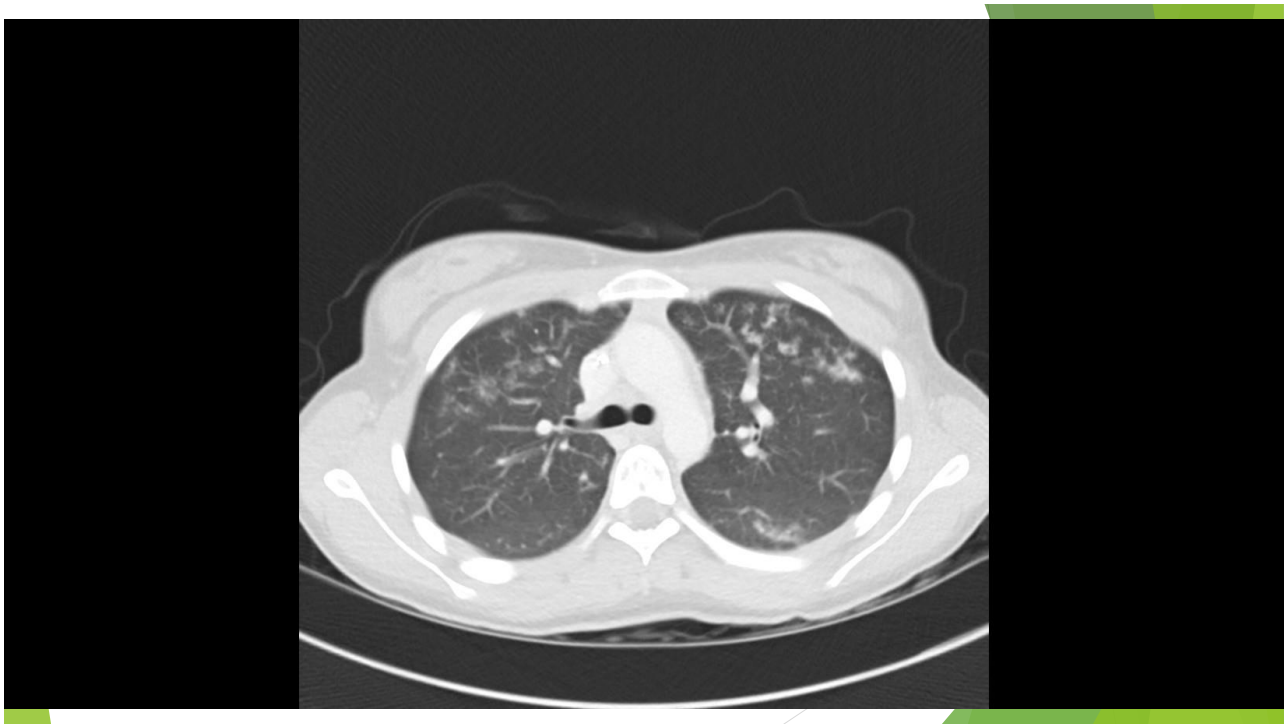
Health Alert: Severe Pulmonary Disease Among People Who Reported Vaping

74

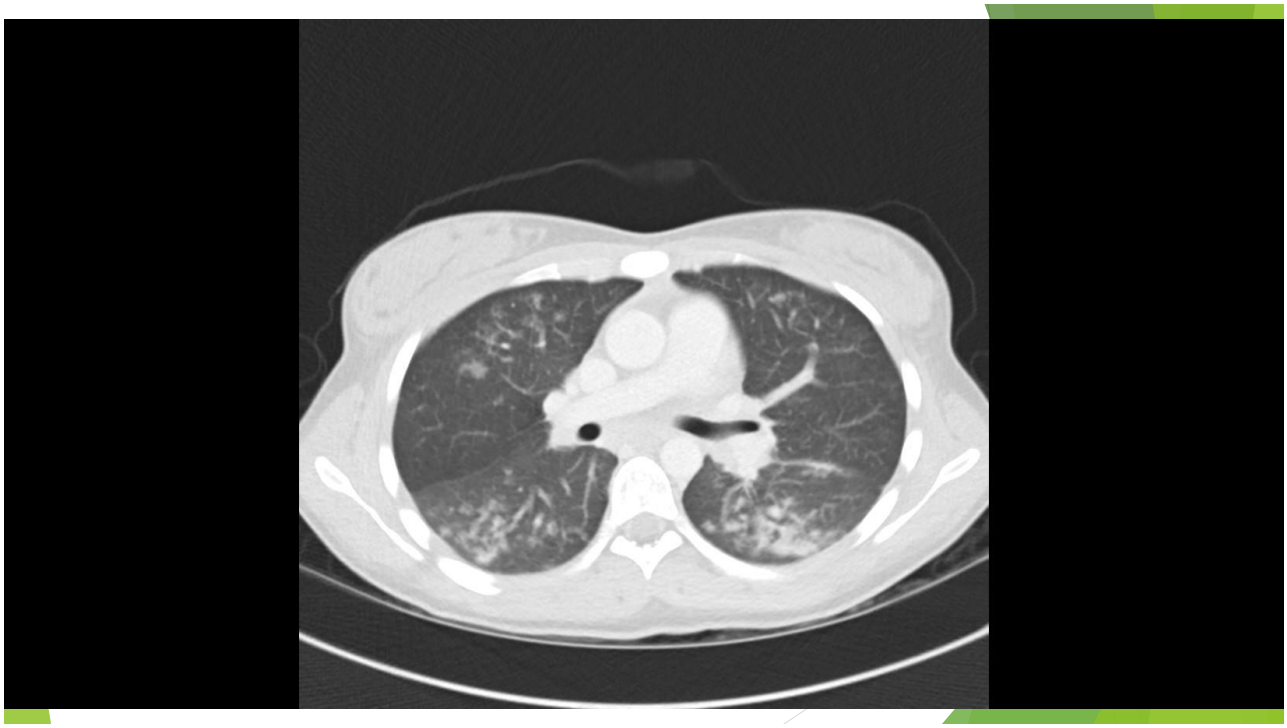
EVALI

- August 2019 – 1st cluster cases of lung injury reported in Wisconsin
- As of February 2758 cases with 64 deaths
- Mostly seen in ages 18 – 34 years – also highest use of marijuana
- 16% of cases were under the age of 18 years
- Most vaping devices contained THC
- Bronchoalveolar lavages showed THC and Vitamin E acetate

75

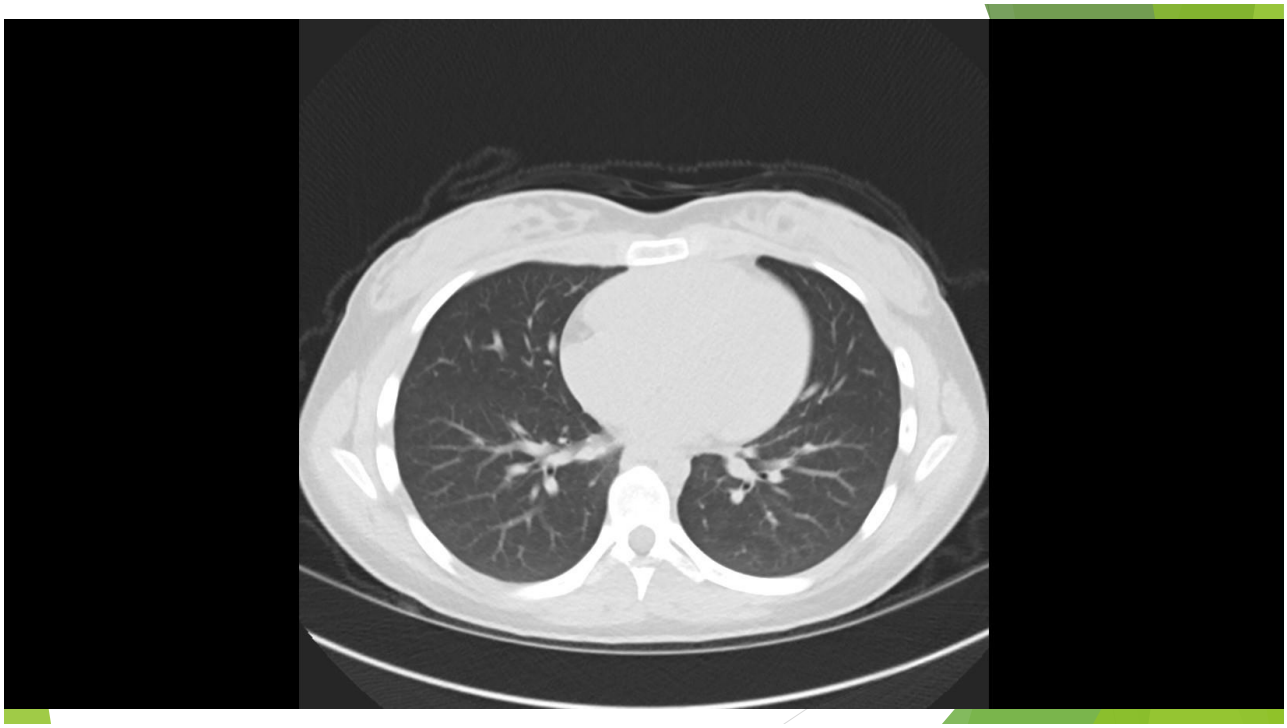


76

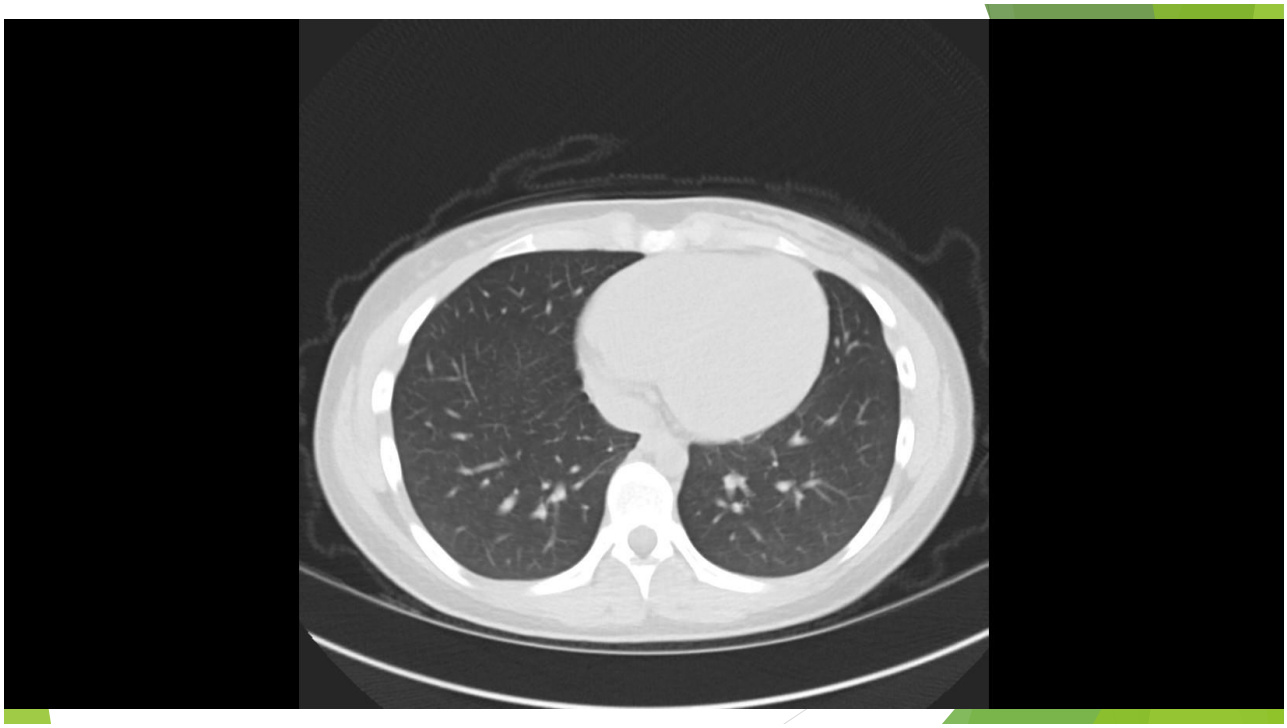


77

78



79



80

Sources

- Biagini Myers, J, et al. A Pediatric Asthma Risk Score to better predict asthma development in young children. J Aller Clin Imm. 2019 May;143(5):1803-1810.e2
- Reddell, H, et al. GINA 2019: a fundamental change in asthma management. European Respiratory Journal. 2019;53: 1901046.
- Committee on Infectious Diseases and Bronchiolitis Guidelines Committee. Updated Guidance for Palivizumab Prophylaxis Among Infants and Young Children at Increased Risk of Hospitalization for Respiratory Syncytial Virus Infection. Pediatrics. August 2014;134 (2) 415-420.
- Aurora, R, et al. Practice Parameters for the Respiratory Indications for Polysomnography in Children. Sleep. 2011; 34(3):379-388.
- American Thoracic Society. Obstructive Sleep Apnea in Children. Am J Respir Crit Care Med. 2009;180:P5-P6.
- Kirk, V, et al. American Academy of Sleep Medicine Position Paper for the Use of a Home Sleep Apnea Test for the Diagnosis of OSA in Children. J Clin Sleep Med. 2017;13(10):1199-1203.
- Liming, BJ, et al. Montelukast and Nasal Corticosteroids to Treat Pediatric Obstructive Sleep Apnea: A Systematic Review Meta-analysis. Otolaryngol Head Neck Surg. 2019;160(4):594-602
- Venekamp, R, et al. Research into Childhood Obstructive Sleep-Disordered Breathing : A Systematic Review. Chest. 2017;152(1).
- Q&A Chest Prognosis for Spontaneous Resolution of OSA in Children. http://www.chestnet.org/News/Blogs/CHEST-Thought-Leaders/2015/11/QA-CHEST- Prognosis-for-Spontaneous-Resolution-of-OSA-in-Children

81

Sources

- Harman, K, et al. Disease-modifying drug therapy in cystic fibrosis. Paediatric Respiratory Reviews. 2017;26(2018):7-9.
- Heijerman, H, et al. Efficacy and safety of the elexcaftor plus tezacaftor plus ivacaftor combination regimen in people with cystic fibrosiss homozygous for the F508 mutation:a double-blind, randomized, phase 3 trial. Lancet. 2019; 394(10212):1940-1948.
- Cystic Fibrosis Foundation. CFTR Modulator Therapies. https://www.cff.org/Life-With-CF/Treatments-and-Therapies/Medications/CFTR-Modulator-Therapies/
- King, B, et al. The EVALI and Youth Vaping Epidemics-Implications for Public Health. NEJM. 2020;382:689-691.
- Outbreak of lung injury associated with eh use of e-cigarette, or vaping, products. Centers for Disease Control and Prevention. Dec 31, 2019. www.cdc.gov/lunginjury

82

Brian Wingrove, MHS, PA-C, DFAAPA

brian.wingrove@choa.org